

**REMARKS**

Reconsideration of this application is respectfully requested. Claims 1-3, 22-24, 31, and 34 have been amended. Claims 4, 20, and 25 have been cancelled without prejudice or disclaimer. Upon entry of the present amendment, claims 1-3, 5, 6, 22-24, 31, and 34-35 will be under examination.

**I. Status of the Claims and Amendments**

Claim 1 has been amended to recite an “estradiol compound or a conjugated equine estrogen composition” instead of “estrogen compound.” Claim 3 has been correspondingly amended. Support for “an estradiol compound” is found throughout the specification, for example, on page 8, lines 19-20, and in a particular example (i.e., 17 $\beta$  estradiol) of original claims 3-4, 20, 22-23, and 34-35. Claim 4 has been cancelled without prejudice or disclaimer. Support for “a conjugated equine estrogen composition” is found at least in original claims 4 and 31.

Claim 2 has been amended to recite “A $\beta$ ” instead of “amyloid- $\beta$ ” for consistency with the nomenclature of claim 1. This amendment is not related to any reason related to patentability.

Claims 20 and 25 have been cancelled without prejudice or disclaimer. Consequently, the dependencies of claims 22-24, 31, and 34 have been amended. Claim 24 has also been amended to recite that “the animal exhibits Alzheimer’s disease symptoms” instead of “wherein the disease or disorder associated with amyloidosis is Alzheimer’s disease.” Support for this amendment may be found at least on page 18, lines 8-17 of the specification.

It is believed that the present amendments are in compliance with 37 C.F.R. § 1.116 since no new searching is necessary, and the present amendments are believed to place the claims in condition for allowance. No new matter is added by way of these amendments.

## II. Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1, 2, 4-6, 20, 22-25, and 31 under 35 U.S.C. § 112, first paragraph, as lacking enablement based on various grounds, has been maintained. The rejection is respectfully traversed, and reconsideration in view of the present amendments is requested.

The Examiner states that the specification does not enable the method of claim 1 because there is no evidence that *in vivo* administration of *any estrogen compound* can reduce A $\beta$  levels without affecting sAPP levels. However, the Examiner acknowledges that this method is enabled with respect to 17 $\beta$ -estradiol. *See* Office Action at pp. 2-3. The Examiner also states that undue experimentation would be required to identify estrogen compounds that reduce A $\beta$  levels without affecting sAPP levels. Applicants maintain that the specification describes how to make and use all the estrogen compounds of the invention, and provides disclosure of pharmaceutical formulations, administration, dosage, and regimen. *See, e.g.*, page 15, line 10 through page 19, line 27.

However, in order to expedite prosecution of the present case, and without conceding the Examiner's position or the validity of the rejection, claim 1 has been amended to recite "an estradiol compound or a conjugated equine estrogen composition" instead of "an estrogen compound." Claim 3 has been amended accordingly. Claims 4, 20, and 25 have been cancelled without prejudice or disclaimer, and the dependencies of claims 22-24, 31, and 34 have been amended.

Estradiol is a species of the genus "estrogen compound" and finds support at least on page 8, lines 19-20 of the specification. The Examiner concedes that the specification is enabling for estradiol effects on A $\beta$  peptide levels without affecting the level of soluble APP (*see* Office Action at page 3). Similarly, the specification enables the use of conjugated equine estrogen compositions, which find support at least on page 8, lines 16-17 of the specification and in original claims 4 and 31. Thus, the specification provides adequate guidance for determining the amount of an estradiol compound or a conjugated equine estrogen composition that reduces A $\beta$  levels *in vivo* without affecting sAPP levels.

The Examiner also states that the specification does not disclose how to predict susceptibility to Alzheimer's Disease (AD) and how the treatment of these individuals with estrogens would delay or reduce the likelihood or ameliorating Alzheimer's Disease or other diseases involving amyloidosis. Applicants maintain that the specification expressly defines "has an increased risk of developing" and "shows a symptom of" a disease or disorder associated with amyloidosis (page 18, lines 8-17). These definitions describe subjects susceptible to developing AD, such as those with a genetic predisposition to develop amyloidosis, or those in their 70s and 80s. Thus, the specification provides adequate guidance for predicting AD susceptibility.

However, in order to expedite prosecution of the present case, claim 20 has been cancelled, and the dependencies of claims 22-24, 31, and 34 have been appropriately amended. The Examiner's statements regarding Zandi et al. (*JAMA*, 288(17):2123-29 (2002)) in the context of prevention of AD and the unpredictability of ameliorating AD are moot in view of the present amendments.

In view of the foregoing, Applicants submit that the present specification fully enables one of ordinary skill in the art to make and use the invention called for in the pending claims without undue experimentation. Thus, it is believed that the basis for the rejections under 35 U.S.C. § 112, paragraph one, enablement, have now been obviated. Applicants therefore respectfully request that these rejections be withdrawn.

### III. Rejections Under 35 U.S.C. § 102(b)

The rejection of claims 20 and 22-25 under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 5,554,601 (“the ‘601 patent”) has been maintained. According to the Examiner, the ‘601 patent discloses a method of treating a neurodegenerative disorder by administering 17 $\beta$ -estradiol. Additionally, the Examiner contends that “the mechanism by which estradiol exerts its activity has no patentable significance.”

The rejection is respectfully traversed, and reconsideration is requested in view of the present amendments.

In order to expedite prosecution of the present case, and without conceding the Examiner's position or the validity of the rejection, Applicants have cancelled claims 20 and 25 without prejudice. Consequently, claims 22-23 have been amended to depend from claim 3, and claim 24 has been amended to depend from claim 1. The '601 patent does not teach methods of lowering A $\beta$  peptides *in vivo* without affecting sAPP levels. In view of the foregoing, the rejection of claims 22-24 in view of '601 is moot. Thus, it is respectfully submitted that the '601 patent does not anticipate amended claims 22-24. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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The rejection of claims 20 and 23-25 under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 5,719,137 ("the '137 patent") has been maintained. The Examiner states that the '137 patent discloses a method of reducing the risk of AD by administering 17 $\alpha$ -dihydroequilenin, and describes an animal study in which groups of rats were treated with 17 $\beta$ -estradiol for up to three days.

The rejection is respectfully traversed, and reconsideration is requested in view of the present amendments.

As set forth above, Applicants have cancelled claims 20 and 25 without prejudice. Consequently, claims 22-23 have been amended to depend from claim 3, and claim 24 has been amended to depend from claim 1. The '137 patent does not teach methods of lowering A $\beta$  peptides *in vivo* without affecting sAPP levels. In view of the foregoing, the rejection of claims 22-24 in the context of reducing the risk of AD by administering 17 $\alpha$ -dihydroequilenin or 17 $\beta$ -estradiol is moot. Thus, the '137 patent does not anticipate amended claims 23-24. Accordingly, applicant respectfully requests that this rejection be withdrawn.

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The rejection of claims 1-3, 5, 6, 20, 23-25, and 31 under 35 U.S.C. § 102 as anticipated by International Publication No. WO 98/43647 ("WO '647") has been maintained. According to the Examiner, WO '647 teaches the administration of 17 $\beta$ -estradiol to reduce APP



In contrast to the above studies, the present invention, as disclosed herein, concerns the expression, formation, or synthesis of APP.

APP holoprotein is a full-length, native peptide of 770 amino acids that has not undergone any proteolytic cleavage. APP holoproteins and APP isoforms are not A $\beta$  peptides. A $\beta$  peptides are generated by proteolytic processing of APP through  $\beta$ - and  $\gamma$ -secretase activities (See Specification at p. 1, line 11 to p. 2, line 9). WO '647 describes several APP isoforms, ranging in size from 695-770 amino acids, that are produced by differential splicing of a primary transcript of the three major APP isoforms, APP-695 (predominantly expressed in neurons), APP-751, and APP-770 (predominantly expressed in astrocytes). See WO'647 at page 3, lines 3-13. These isoforms are not A $\beta$  peptides and in particular not A $\beta$ 40 or A $\beta$ 42 peptides (which are 40 or 42 amino acids in length, respectively).

For the Examiner's convenience and reference, Applicants are providing a copy of a description of APP and Alzheimer's authored by Dr. Joe Buxbaum (a neuroscientist skilled in the art, from website: [http://www.upstate.com/features/app\\_lp.asp?c=221&r=556](http://www.upstate.com/features/app_lp.asp?c=221&r=556)), describing the relationship of APP to A $\beta$ , and the complex cleavage and regulatory processes involved in generating various APP isoforms.

Importantly, the only reference in WO '647 of any APP fragments is the hypothetical statement in the Abstract, at lines 4-5 that "[t]he reduction in the level of APP holoprotein caused by estrone or 17 $\beta$ -estradiol is also expected to reduce the production of neurotoxic APP fragments." Nowhere in WO'647 is there any teaching of reducing A $\beta$  levels, without affecting sAPP levels.

Furthermore, a reduction of APP holoprotein is not indicative of reduced A $\beta$  levels. In fact, the present specification states that "a change in sAPP $\alpha$  levels (up or down) is a poor guide to anti-amyloid drug development", and describes the present inventors' surprising discovery that administration of estrogen compounds reduces A $\beta$  levels, without affecting sAPP levels (p. 7, lines 15-22). Thus, reduced APP holoenzyme levels do not necessarily correlate to reduced A $\beta$  levels.

Applicants point out that WO '647 makes no mention of A $\beta$  levels, much less the ratios of A $\beta$ 42 to A $\beta$ 40 in the context of reducing synthesis or production of APP holoenzyme; and therefore, cannot anticipate the presently claimed methods that require a reduction in A $\beta$  levels while not affecting sAPP levels. Even assuming *arguendo*, that WO'647 describes APP fragments that could encompass A $\beta$ s, reducing the *production* of APP holoenzyme does not equate with reducing A $\beta$  levels *in vivo* in an animal, without affecting soluble APP levels.

In view of the foregoing, WO '647 does not anticipate pending claims 1-3, 5, 6, 23-24, and 31 and Applicants respectfully request that this rejection be withdrawn.

#### IV. Rejections Under 35 U.S.C. § 103(a)

Claim 22 has been rejected under 35 U.S.C. § 103(a) as obvious over the '137 patent or WO '647. The Examiner acknowledges that each of these references fails to disclose administration of 17 $\beta$ -estradiol for at least 10 days, but contends that this dosing regimen would be obvious to one of ordinary skill. The Examiner also reiterates his contention that the mechanism of action of estradiol is not significant.

The rejection is respectfully traversed, and reconsideration is requested in view of the present amendments.

Claim 22 has been amended to depend from claim 1. Neither '137 nor WO '647 teaches or suggests an A $\beta$  level reducing dose of 17 $\beta$ -estradiol that does not affect soluble APP levels. Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. Neither of the cited references alone or in combination disclose or suggest the instant invention because they do not disclose or suggest, and therefore cannot render obvious the presently claimed methods that require a reduction in A $\beta$  levels while not affecting sAPP levels. Thus, these references (taken alone or in combination) do not teach or suggest the presently claimed method for reducing A $\beta$  levels *in vivo* without affecting sAPP levels.

In view of the foregoing, the rejection of claim 22 as obvious over the '137 patent or WO '647 is moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.





rejections (WO '488 in view of the '342 patent, the '662 patent or Lundeen) provide any teaching or suggestion of presently claimed *in vivo* methods for reducing A $\beta$  levels with an amount of estradiol or conjugated equine estrogen composition that would exhibit the property of not affecting soluble APP levels. Importantly, the claim element cannot be ignored, as courts have repeatedly held that "[i]t is elementary patent law that all limitations are material." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 42 USPQ2d 1257 (Fed. Cir. 1997).

The WO '488 publication discloses that cholesterol lowering drugs can reduce production of A $\beta$ . WO'488 does not teach that A $\beta$  levels can be reduced according to the present invention without affecting sAPP levels *in vivo*. Furthermore, the correlation between lowering cholesterol and A $\beta$  formation is weak at best. In particular, Applicants note that Fagan *et al.* ((2004) *American Journal of Pathology* Vol. 165, No. 4:1413; copy previously provided) showed that there were "no differences in the A $\beta$  pathology in PDAPP mice of various apoAI genotypes despite robust differences in plasma cholesterol levels between the groups" (see Fagan *et al.*, Abstract).

The deficiencies of WO '488 cannot be overcome by combining the general teachings of the '342 patent, the '662 patent, or Lundeen, that merely teach the interchangeability of estradiol and equine conjugated estrogen.

Furthermore, the Examiner has not provided any evidence to suggest that any of these references inherently teaches or suggests that using estradiol as claimed would exhibit the property of reducing A $\beta$  levels without affecting soluble APP levels *in vivo*. On the contrary, the only evidence of record concerning *in vivo* methods for reducing A $\beta$  levels without affecting soluble APP levels is that set forth in the present application.

The use of the disclosure of the present application (*i.e.*, *in vivo* methods for reducing A $\beta$  levels without affecting soluble APP levels as an inherent property of the claimed invention) to dismiss the objective evidence, and thereby to support the *prima facie* case for obviousness, represents an improper "hindsight" argument for obviousness. See for example, *In re Adams* 356 F.2d 998 (CCPA 1962), 148 USPQ 742. The *In re Adams* court held that it was not possible to



In view of the foregoing, claims 1-6, 20, 22-25, and 31 are not obvious over WO '488 in view of the '342 patent, the '662 patent or Lundeen. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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Claim 4 has been rejected under 35 U.S.C. § 103(a) as obvious over WO '647 in view of the '601 patent. WO '647 discloses a method for treating neurodegenerative disorders by reducing APP holoprotein levels using 17 $\beta$ -estradiol. The '601 patent is cited by the Examiner as teaching the equivalence of 17 $\beta$ -estradiol and conjugated equine estrogen, as called for in claim 4. According to the Examiner, it would have been obvious to replace 17 $\beta$ -estradiol with conjugated equine estrogen in view of these references.

The rejection is respectfully traversed, and reconsideration is requested.

Claim 1 has been amended to incorporate the subject matter of claim 4, and claim 4 has been cancelled without prejudice or disclaimer. Thus, the rejection of claim 4 would apply to amended claim 1. As set forth in detail above, neither WO '647 nor the '601 patent discloses A $\beta$  levels.

Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. None of the cited references alone or in combination disclose or suggest the instant invention because they do not disclose or suggest, and therefore cannot render obvious the presently claimed methods that require a reduction in A $\beta$  levels while not affecting sAPP levels. Thus, these references (taken alone or in combination) do not teach or suggest the presently claimed method for reducing A $\beta$  levels *in vivo* without affecting sAPP levels.

In view of the foregoing, claim 4 is not obvious over WO '647 in view of the '601 patent. Accordingly, Applicants respectfully requests that this rejection be withdrawn.


**Conclusion**

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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